REMARKS

Status of the Claims

Claims 1, 7-9, 13 and 17 have been amended. Support for the amendments can be found throughout the present specification and claims as originally filed, e.g., at page 7, lines 8-14. Claims 4, 5, 10 and 15 have been cancelled without prejudice or disclaimer. No new matter has been added.

Now pending are claims 1, 7-9, 13, 14, 16, and 17.

Rejections under 35 U.S.C. §112, second paragraph

In the Office Action, claims 9 and 17 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. This rejection is traversed.

While Applicants do not agree with the rejection, claims 9 and 17, as amended, recite that the adhesive layer comprises "one or more components" selected from those recited. Applicants respectfully contend that this language is clear and is not indefinite. Reconsideration and withdrawal of the rejection is proper and such action is requested.

Rejections under 35 U.S.C. §103(a)

In the Office Action, claims 1, 7 and 10 stand rejected as unpatentable over Patel et al. (U.S. Patent No. 5,340,572). As noted above, claim 10 has been cancelled, so the rejection thereof is moot. As to the remaining claims, this rejection is traversed.

According to the Office Action, Patel "[teaches] a topical gel composition containing medicaments . . . . Diclofenac is disclosed . . . . [t]he compositions can include salts and buffers such as ammonium chloride . . . Sustained efficacy is disclosed." Office Action at page 4. The Office Action concludes, "It would have been obvious . . . to formulate sodium diclofenac and ammonium chloride in the gel suspension of Patel et al." Applicants respectfully disagree.

As an initial matter, it must be pointed out that Patel is directed to aqueous ophthalmic gels having a particular osmotic pressure, not to a non-aqueous patch as in the present claims.

In addition, although Patel mentions in passing the use of "diclofenac," Applicants respectfully contend that Patel does not disclose the use of sodium diclofenac as recited in the present claims. It will be appreciated that diclofenac and sodium diclofenac are different and may have different properties; for example, the absorbability of the two materials in a percutaneously absorbable preparation is not the same. Although the Office Action states that "the sodium salt of diclofenac is taught by Patel et al." (Office Action at page 7), the Office Action provides no evidence for this statement. Even if Patel teaches that "pharmaceutically acceptable salts of the medicament can be utilized" (Office Action at page 7), nowhere does Patel teach or suggest the specific sodium salt of diclofenac (as opposed to other salt forms or the free acid of diclofenac). Applicants contend that Patel does not teach or suggest (i) non-aqueous formulations (as required by the instant claims) or (ii) specific salt forms of acid drugs (e.g., sodium diclofenac).

Furthermore, while the Office Action refers to Patel at column 9, lines 27-28 as disclosing "buffers and salts . . . in amount from about 0.01-5%," Applicants point out that the cited portion of Patel does not disclose the use of ammonium chloride as cited by the Examiner. Indeed, column 9, lines 27-28 of Patel refer to medicaments, not buffers and salts (Column 8, lines 26-28 of Patel refers to amounts of sodium chloride used to provide a desired osmolality). The only mention of ammonium chloride in Patel is in a listing of buffers at column 8, lines 14-15 (where no amounts are provided). In fact, Patel, at column 8, lines 30-39, provides that:

> Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfite and the like, e.g., potassium chloride, sodium thiosulfate, sodium

> metabiosulfite, sodium bisulfite, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated ranges.

Applicants submit that this generalized recitation of cations and anions, and certain specific salts other than ammonium chloride, does not constitute a disclosure of ammonium chloride. The list of possible cations and anions in the above-quoted passage is large (i.e., at least potassium, ammonium, and sodium as cations, and at least 10 recited anions). This general disclosure, with a large number of possible combinations and no specific disclosure of ammonium chloride, does not (contrary to the Office Action) teach or suggest the specific salt, ammonium chloride, especially in view of the statement in Patel that "sodium chloride is preferred" (Col. 8, line 24).

The salts disclosed at the cited portion of Patel are used to provide a desired osmolality of the ophthalmic formulation. Applicants contend that such a disclosure is not relevant to the absorbability of sodium diclofenac, and is not relevant to the patentability of the present claims. Indeed, one of ordinary skill in the art would not be motivated to select the specific combination of sodium diclofenac and ammonium chloride, in the recited amounts, as required by the pending claims.

Moreover, while Applicants contend that the Office Action has failed to make out a prima facie case of obviousness of the pending claims, Applicants submit that any *prima facie* case of obviousness is rebutted by evidence of the unexpected properties of the claimed percutaneous preparations. As seen from the Examples provided in the specification, preparations including ammonium chloride in addition to sodium diclofenac have enhanced skin permeability compared to preparations having no ammonium chloride. See, e.g., Example 4 (about 7-fold increase in skin permeability rate with ammonium chloride compared to Comparative Example 4 without ammonium chloride) and Example 19 (about 4.8-fold increase in skin permeability rate with ammonium chloride compared to Comparative Example 19 without ammonium

chloride). Applicants submit that such unexpectedly superior properties are not and cannot be obvious, and that the presently-claimed preparations (and the methods of new claims 13-17) are not clearly not obvious in view of the cited reference. Although the Office Action appears to give no weight to the evidence of unexpected results as discussed previously, Applicants respectfully contend that the Office must consider all evidence of patentability. According to the MPEP, evidence supporting patentability must be considered in determining issues of obviousness. See, e.g., MPEP 716.01.

For at least the foregoing reasons, Applicants contend that the pending claims are not rendered unpatentable by Patel et al.

In the Office Action, claims 1, 4, 5, and 7-10 stand rejected as unpatentable over Ledger et al. (U.S. Patent No. 5,120,545) in view of Inagi. As noted above, claims 4, 5 and 10 have been cancelled, so the rejection thereof is moot. As to the remaining claims, this rejection is traversed.

According to the Office Action, Ledger "[teaches] a matrix for transdermal administration of a drug . . . Ammonium chloride is specified . . . One specific analgesic agents taught is ketoprofen." Office Action at page 9. The Office Action concludes, "It would have been obvious . . . to combine the teachings of Ledger et al. and Inagi et al. and utilize sodium diclofenac." Office Action at page 10. Applicants do not agree.

As previously noted, Ledger does not disclose ibuprofen or diclofenac, although ketoprofen is mentioned. Ledger mentions ammonium chloride as a weak base to raise the pH within lysosomes, as an antigen processing-inhibiting agent. Ledger discloses only aqueous preparations, and that skin sensitization depends upon the pH of the preparation. Ledger teaches that avoiding a low pH in the formulation is essential to avoid such skin sensitization. Applicants submit that this is not relevant to the presently-claimed subject matter.

The disclosure of Ledger cannot render obvious the presently-claimed non-aqueous patch comprising a matrix. A non-aqueous system, as presently claimed, does not depend on pH values in the way that an aqueous system does. Therefore, the teaching of Ledger (that avoiding low pH is important) cannot render obvious the present claims. Even if Ledger teaches the use of amphiphilic amines in aqueous formulations, Ledger cannot teach or suggest the use of ammonium chloride in a non-aqueous system as presently claimed.

Inagi cannot remedy the deficiencies in the teachings of Ledger. Although the Office Action states that Inagi teaches that ketoprofen and sodium diclofenac are both angelgesic [sic] agents" (Office Action at page 10), Inagi does not teach or suggest the use of sodium diclofenac in a non-aqueous system. Even if Inagi teaches that ketoprofen and sodium diclofenac are both analgesic agents as stated in the Office Action, there would be no motivation to modify the teachings of Ledger to arrive at the presently claimed subject matter.

Furthermore, Inagi is directed to hydrophilic adhesive base materials having excellent mechanical strength and adhesion to skin. There would be no motivation to combine the teachings of Ledger (even if the teachings as were as described by the Examiner) with the teachings of Inagi to arrive at the presently-claimed non-aqueous patch. Ledger and Inagi are directed to different objectives, and there would simply be no reason to combine the references as suggested in the Office Action. Moreover, Applicants submit that there would be no reasonable expectation of success in making such a combination to arrive at the presently-claimed subject matter.

Still further, as discussed above, Applicants submit that any *prima facie* case of obviousness is rebutted by evidence of the unexpected properties of the claimed percutaneous preparations. As discussed above, preparations including ammonium chloride in addition to sodium diclofenac have enhanced skin permeability compared to preparations having no ammonium chloride. Applicants submit that such unexpectedly

superior properties are not and cannot be obvious, and that the presently-claimed preparations (and the methods of claims 13-17) are clearly not obvious in view of the cited references.

For at least the foregoing reasons, Applicants contend that the pending claims are not rendered unpatentable by Ledger or Inagi, alone or in combination.

In the Office Action, claims 1, 4, 5, 7-10, and 13-17 stand rejected as unpatentable over Kawaji et al. (U.S. Patent No. 6,262,121) in view of Arellano (European Journal of Pharmaceutical Sciences) and in further view of Porter et al. (U.S. Patent No. 5,968,533). As noted above, claims 4, 5, 10 and 15 have been cancelled, so the rejection thereof is moot. As to the remaining claims, this rejection is traversed.

According to the Office Action, Kawaji teaches "oil patches containing diclofenac sodium and fatty acids. The diclofenac sodium is admixed in a solution of styrene-isoprene-styrene block copolymer." Office Action at page 13.

As Applicants understand the reference, Kawaji discloses the use of oily patches for external use containing diclofenac sodium, isostearic acid, and a fatty acid. According to Kawaji, combining a fatty acid with diclofenac sodium to produce the free acid of diclofenac (in order to improve transdermal absorption of diclofenac) can result in simultaneous production of the sodium salt of the fatty acid, which can cause skin irritation. (Kawaji, Column 2, lines 24-31.) Kawaji does not teach or suggest the use of sodium diclofenac with an acid addition salt of an amine (including ammonium chloride).

As Applicants understand the reference, Arellano describes aqueous preparations of diclofenac and propylene glycol and/or isopropyl myristate. Thus, Arellano describes percutaneous absorbability of aqueous preparations. Furthermore, it would not be obvious to combine the oily preparations of Kawaji with the aqueous preparations of Arellano.

As Applicants understand the reference, Porter describes skin care transdermal delivery devices including an antioxidant (such as Vitamin C) and a moisturizer (such as hyaluronic acid). Certain water-soluble additives such as polyethylene glycols or ammonium chloride enhance percutaneous absorbability. All the preparations of Porter are aqueous preparations and percutaneous absorbability only in aqueous preparations is disclosed in Porter. In addition, only the enhancement of absorption of antioxidants such as Vitamin C and moisturizers such as hyaluronic acid is disclosed. Porter et al is silent regarding the percutaneous absorbability of salt forms of acid drugs (e.g., sodium diclofenac) in non-aqueous systems as presently claimed.

One of ordinary skill in the art would not be motivated to combine the disclosures of Kawaji (relating to oily preparations) with the disclosures of Arellano and/or Porter (both relating to aqueous preparations). Moreover, one of skill in the art would not have the requisite reasonable expectation of success in making such a combination. Applicants respectfully submit that the presently-claimed subject matter is not and cannot be rendered obvious by any of Kawaji, Arellano, and Porter, whether taken alone or in any combination.

Reconsideration and withdrawal of the rejections is proper and such action is requested.

Double Patenting Rejections

In the Office Action, claims 1, 4, 5, and 7-10 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 10/479,072; claims 1, 4, 5, 7-10 and 13-17 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 10/549,184; claims 1, 4, 5, 7-10 and 13-17 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 10/548,739; claims 1, 4, 5, 7-10 and 13-17 stand provisionally rejected

on the ground of obviousness-type double patenting over certain claims of co-pending application no. 11/596,605; and claims 1, 4, 5, 7-10 and 13-17 stand provisionally rejected on the ground of obviousness-type double patenting over certain claims of co-pending application no. 10/258,022.

As an initial matter, as noted above, claims 4, 5, 10 and 15 have been cancelled, so the rejection thereof is moot.

In addition, Applicants note that the mention of co-pending application no. 10/548,739 is apparently incorrect; possibly the Examiner intended to refer to USSN 10/584,739. Clarification is requested.

Still further, the Office Action refers to claims 16-21 of USSN 10/549,184; however, USSN 10/549,184 does not include claims 16-21 (and apparently has never had such claims). Clarification is requested.

Without agreeing with any of the double patenting rejections, Applicants point out that each of the rejections is provisional, and that the corresponding claims have not yet been patented. Applicants respectfully request that any provisional double patenting rejections be deferred until the present application is otherwise in condition for allowance.

Reconsideration and withdrawal of the rejections is proper and the same is requested.

Conclusion

For at least the foregoing reasons, Applicants request reconsideration of the application. Early and favorable action is requested.

Applicants request any extension of time necessary for consideration of this response. If for any reason a fee is required, a fee paid is inadequate or credit is owed

for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**, under Reference No. 56769 (71526), Customer No. 21874.

Respectfully submitted,

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